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A convenient one-pot synthesis of 2-(alkylthio)isoflavones from deoxybenzoins using a phase transfer catalyst

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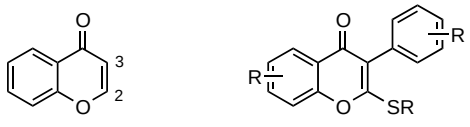
Abstract—A convenient phase transfer catalysis procedure for the synthesis of 2-(alkylthio)isoflavones is described. A number of compounds of potential pharmaceutical interest can be prepared in a single step at ambient conditions from various, easily accessible deoxybenzoins using this method.

The 4*H*-1-benzopyran-4-one ring system (**1**, Fig. 1) is widely found in a number of natural products such as flavonoids. These natural products have demonstrated numerous biological activities such as antiviral, anti-inflammatory, antiallergic, antimutagenic and anticarcinogenic activities.[1]

This fact has led us to investigate novel 4*H*-1-benzopyran-4-one derivatives as new therapeutic agents for hormone-dependent breast cancer.[2] As part of this effort, we have been interested in 3-aryl-2-alkylthio-4*H*-1-benzopyran-4-ones, or 2-(alkylthio)isoflavones (**2**, Fig. 1), as potential drug candidates in this area. However, only a few methods have been reported for the synthesis of 2-alkylthio-4*H*-1-benzopyran-4-ones.[3] Furthermore, these methods suffer several disadvantages such as low yields, multiple steps, and harsh conditions. Recently, a high yielding one-pot synthesis of 2-methylthio-4*H*-1-benzopyran-ones has been reported using KHMDS as a base.[4] However, this method also requires skillful handling of the base, low temperature, and anhydrous reaction conditions. Herein we report a convenient and efficient synthesis of 2-(alkylthio)-isoflavones under ambient conditions using a phase transfer catalyst.



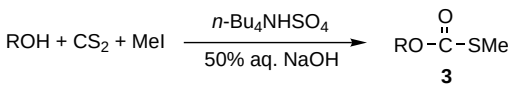
4*H*-1-benzopyran-4-one, **1** 2-(alkylthio)isoflavone, **2**

Figure 1.

Several years ago a phase transfer catalysis procedure was reported for the synthesis of *O*-alkyl-*S*-methyl dithiocarbonates (**3**) in high yields (Scheme 1).[5] We investigated this procedure for the synthesis of 2-(alkylthio)isoflavones (**2**) from deoxybenzoins since we envisioned that the *O*-aryl-*S*-alkyl dithiocarbonates would be good intermediates. More importantly, because deoxybenzoins have an active methylene group, it was expected that the *O*-aryl-*S*-alkyl dithiocarbonates **3′** would undergo further cyclization reaction in this reaction condition, thereby directly generating the desired 2-(alkylthio)isoflavones **2** in a single step (Scheme 2).

Deoxybenzoins **6** were prepared by Friedel–Crafts acylation of resorcinol with corresponding arylacetic acids followed by Mitsunobu reaction for the selective methylation of 4-hydroxyl group (Scheme 3).[6]

As expected, when the deoxybenzoin **6a**, carbon disulfide, and methyl iodide in a THF[7]/water two-phase system were treated with aqueous NaOH solution at room temperature in the presence of 10 mol% of tetrabutylammonium hydrogensulfate (n-$Bu_4N{\cdot}HSO_4$), the



Scheme 1.

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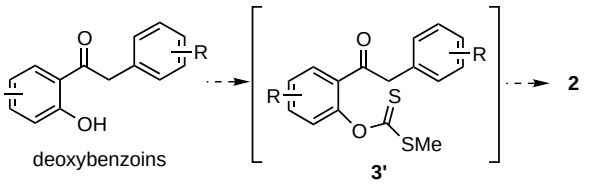
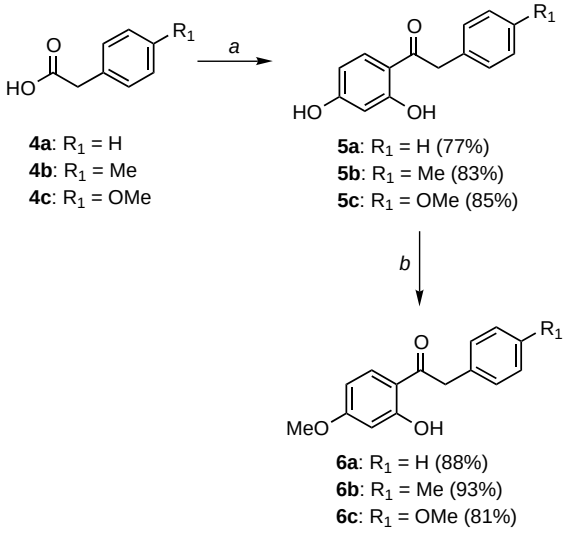


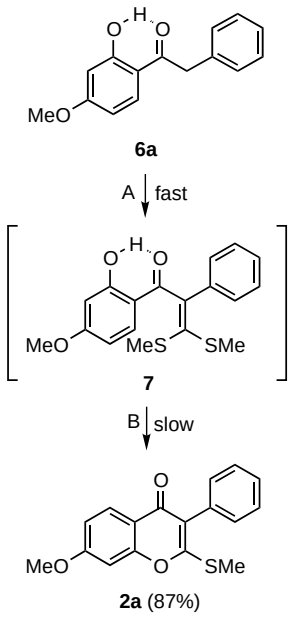
Scheme 2.



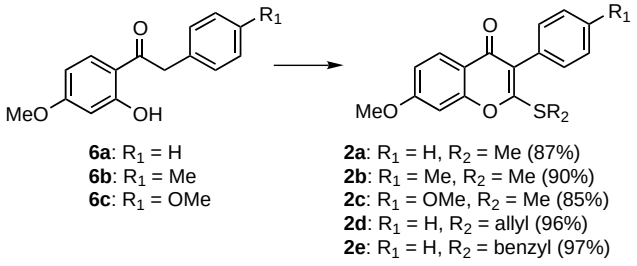
Scheme 3. *Reagents and conditions*: (a) resorcinol, $BF_3{\cdot}OEt_2$, 100°C, 2 h; (b) PPh_3, DIAD, MeOH, THF, rt, 5 min; (c) CS_2, R_2X, n-$Bu_4N{\cdot}HSO_4$, aq. NaOH, THF, rt, 3–7 h.

desired 2-(methylthio)isoflavone **2a** was obtained in 87% yield (Scheme 4). The reaction apparently occurred in a stepwise manner as monitored by TLC. Interestingly, the spectral data of the intermediate indicated that the reaction proceeded not via the *O*-alkyl-*S*-methyl dithiocarbonate but via α-oxoketene dithioacetal (**7**).[8] This could be explained by the intramolecular hydrogen bond of the starting deoxybenzoin, which might facilitate the enolate formation. In addition, the formation of α-oxoketene dithioacetal intermediate (step A, Scheme 3) is very fast; all the starting material was converted into the intermediate as soon as the aqueous NaOH solution was added. However, when the reaction is done at 0°C, intermediate **7** can be obtained within 5 min in a high yield (>90%). In contrast, the subsequent cyclization (step B, Scheme 3) is the rate-determining step, and thereby requires a longer reaction time (3–4 h) to be completed presumably because the intramolecular hydrogen bond of intermediate **7** is still rigid. However, this reaction can be completed within an hour when the reaction mixture is warmed at ~50°C.

Similar results were obtained when deoxybenzoin **6b** and **6c** were used as starting materials (Scheme 5). Therefore, this method proved to be efficient to prepare the 2-(methylthio)isoflavones, which can be used as useful intermediates to introduce various nucleophiles at the 2-position. In addition, as shown in Scheme 5, this process was also efficient when different alkyl



Scheme 4. *Reagents and conditions*: CS_2, R_2X, n-$Bu_4N{\cdot}HSO_4$, aq. NaOH, THF, rt, 3 h.



Scheme 5. *Reagents and conditions*: CS_2, R_2X, n-$Bu_4N{\cdot}HSO_4$, aq. NaOH, THF, rt, 3–7 h.

halides were used as an alkylating agent, indicating diverse alkylthio groups can be directly introduced at the 2-position using this process.

In summary, we have described a convenient phase transfer catalysis procedure allowing the efficient conversion of deoxybenzoins into 2-(alkylthio)isoflavones in a single step at ambient reaction conditions. This method can be very useful to generate a number of drug-like compounds from easily available deoxybenzoins in a short period of time. Extended studies on reaction scopes and applications of this method are currently underway.

General experimental procedure

To a stirred mixture of a deoxybenzoin (1 mmol), carbon disulfide (0.6 mL, 10 mmol), alkyl halide (2.2 mmol), and tetrabutylammonium hydrogensulfate (34 mg, 0.1 mmol) in THF (3 mL) and water (1 mL) was slowly added aqueous NaOH solution (1.2 mL, 12 mmol, 10 M) at room temperature. A slight exothermic reaction and a color change of the mixture were observed. The resulting mixture was vigorously stirred

at room temperature for several hours, and the product was extracted with ethyl acetate (2×10 mL). The separated organics were washed with water (10 mL) and then with brine (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluting with EtOAc/hexane or MeOH/$CHCl_3$) to give the product as a white solid. All the products were recrystallized from EtOAc/hexane.[9]

Acknowledgements

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6. (a) For the reaction conditions for the synthesis of compounds **5**, see: Wähälä, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005; (b) Compounds **6a** and **6c** are commercially available; (c) Physical and spectral data for compound **6b**: mp 71–72°C; IR (KBr) 1639, 1623, 1516, 1508, 1439, 1388, 1355, 1268, 1231, 1205, 1131 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.73 (d, $J=8.6$ Hz, 1H), 7.14–7.24 (m, 4H), 6.43–6.40 (m, 2H), 4.15 (s, 2H), 3.81 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.63, 166.56, 166.28, 137.14, 132.47, 131.71, 129.87, 129.61, 113.60, 108.20, 101.43, 55.98, 44.89, 21.48; HRMS calcd for $C_{16}H_{16}NaO_3$ $(M+Na)^+$ 279.0997, found 279.0989.
7. We have modified the original reaction condition by using THF as an organic solvent instead of carbon disulfide.
8. NMR data for compound **7**: ^1H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H), 7.56 (d, $J=8.6$ Hz, 1H), 7.43–7.45 (m, 2H), 7.27–7.35 (m, 3H), 6.39–6.43 (m, 2H), 3.80 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.21, 166.71, 166.46, 143.82, 137.06, 136.34, 134.11, 129.21, 128.96, 128.83, 113.88, 108.40, 101.43, 56.03, 18.05, 17.28.
9. Physical and spectral data for compounds **2**: (a) **2a**: mp 140–142°C; IR (KBr) 1629, 1619, 1584, 1541, 1499, 1431, 1373, 1349, 1252, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, $J=8.9$ Hz, 1H), 7.32–7.44 (m, 5H), 6.96 (dd, $J=8.9$, 2.4 Hz, 1H), 6.84 (d, $J=2.3$ Hz, 1H), 3.91 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.96, 164.41, 164.01, 158.52, 132.64, 131.05, 128.88, 128.68, 128.34, 122.29, 117.66, 114.62, 100.10, 56.30, 14.12; HRMS calcd for $C_{17}H_{15}O_3S$ $(M+H)^+$ 299.0742, found 299.0735. (b) **2b**: mp 188–189.5°C; IR (KBr) 1632, 1612, 1544, 1510, 1433, 1368, 1287, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $J=8.9$ Hz, 1H), 7.20–7.26 (m, 4H), 6.95 (dd, $J=8.9$, 2.3 Hz, 1H), 6.83 (d, $J=2.3$ Hz, 1H), 3.90 (s, 3H), 2.53 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.08, 164.20, 163.96, 158.51, 138.50, 130.84, 129.68, 129.58, 128.36, 122.24, 117.66, 114.55, 100.08, 56.28, 21.85, 14.14; HRMS calcd for $C_{18}H_{16}NaO_3S$ $(M+Na)^+$ 335.0718, found 335.0721. (c) **2c**: mp 169–170°C; IR (KBr) 1616, 1540, 1437, 1374, 1348, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $J=8.8$ Hz, 1H), 7.24–7.27 (m, 2H), 6.93–6.96 (m, 3H), 6.83 (d, $J=2.3$ Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.15, 164.31, 163.95, 159.90, 158.50, 132.24, 128.32, 124.69, 121.82, 117.61, 114.57, 114.40, 100.07, 56.28, 55.65, 14.15; HRMS calcd for $C_{18}H_{16}NaO_4S$ $(M+Na)^+$ 351.0667, found 351.0668. (d) **2d**: mp 117–118°C; IR (KBr) 1635, 1615, 1585, 1546, 1503, 1435, 1373, 1345, 1252, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, $J=8.9$ Hz, 1H), 7.30–7.44 (m, 5H), 6.96 (dd, $J=8.9$, 2.4 Hz, 1H), 6.81 (d, $J=2.3$ Hz, 1H), 5.83–5.94 (m, 1H), 5.27 (dd, $J=16.9$, 1.2 Hz, 1H), 5.14 (dd, $J=10.1$, 0.8 Hz, 1H), 3.91 (s, 3H), 3.70 (d, $J=6.9$ Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.21, 164.12, 163.40, 158.50, 133.20, 132.61, 131.08, 128.82, 128.68, 128.39, 123.35, 119.27, 117.69, 114.51, 100.13, 56.31, 34.54; HRMS calcd for $C_{19}H_{16}NaO_3S$ $(M+Na)^+$ 347.0718, found 347.0705. (e) **2e**: mp 153–154°C; IR (KBr) 1636, 1617, 1586, 1546, 1502, 1438, 1373, 1341, 1252, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $J=8.9$ Hz, 1H), 7.22–7.41 (m, 10H), 6.95 (dd, $J=8.9$, 2.4 Hz, 1H), 6.81 (d, $J=2.3$ Hz, 1H), 4.30 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.22, 164.10, 163.54, 158.48, 136.51, 132.52, 131.04, 129.32, 129.17, 128.81, 128.66, 128.39, 128.17, 122.97, 117.70, 114.49, 100.19, 56.31, 36.17; HRMS calcd for $C_{23}H_{18}NaO_3S$ $(M+Na)^+$ 397.0874, found 397.0856.